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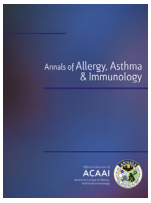

Efficacy and safety of a novel nasal steroid, S0597, in patients with seasonal allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) poses a significant global burden with increasing prevalence. Although intranasal glucocorticosteroids are effective, older agents can have limiting side effects. S0597, a novel intranasal glucocorticosteroid, has demonstrated good safety and tolerability during preclinical and phase 1 studies.
Objective: To assess the clinical efficacy, safety, and tolerability of different doses of S0597 nasal spray vs placebo in patients with seasonal AR.
Methods: This phase 2, randomized, double-blinded, placebo-controlled, parallel-group, single-center study randomized 159 patients 18 to 65 years old (mean age 37.8 years) with a positive skin prick test reaction for *Dactylis glomerata* to receive S0597 at 200, 400, or 800 μg/d or placebo for 15 days. On days 1 (baseline), 15, and 16, patients underwent a 4-hour pollen challenge to evaluate treatment efficacy measured by the change in total nasal symptom score (TNSS) from baseline to days 15 and 16 and changes in TNSS subscales and nasal secretion.
Results: Statistically significant improvements in TNSS from baseline to days 15 and 16 were observed with all S0597 doses vs placebo ($P = .0005$ overall), with the greatest improvements observed in the highest-dose group ($P < .0001$). Significant decreases were observed in each S0597 dose group vs placebo for TNSS subscales and nasal secretion. Improvements in nasal secretion were related to dose, with the greatest decreases from baseline in the 800-μg/d group on days 15 and 16 ($P < .0001$).
Conclusion: Treatment with S0597 at 200, 400, and 800 μg/d by 2 divided doses for 2 weeks was safe and significantly more effective than placebo for improving nasal symptoms associated with grass pollen-induced seasonal AR in adults.
Trial Registration: ClinicalTrials.gov, identifier NCT01614691.

Introduction

Allergic rhinitis (AR) is a significant public health concern affecting an estimated 500 million people globally.[1,2] Intranasal glucocorticosteroids (INSs) are regarded as the most effective pharmacologic treatment for AR and are recommended by the Allergic Rhinitis and its Impact on Asthma guidelines as first-line treatment.[2,3] INSs have a good safety profile, with a low risk of systemic side effects owing to their low systemic bioavailability.[4] This is especially true for newer INSs, such as ciclesonide, mometasone furoate, and fluticasone furoate, which have a systemic bioavailability lower than 1%.[5]

S0597 is a novel INS developed by the Sun Pharma Advanced Research Company Ltd (Mumbai, India). S0597 has potent glucocorticoid receptor binding (in the nanomolar range) and low binding affinity to other sex steroid receptors (including progesterone, estrogen receptors [ERa and ERb], and testosterone) and aldosterone.[6] In preclinical models, S0597 showed local anti-inflammatory activity, low oral bioavailability, and low potential for systemic adverse effects, leading to a high therapeutic index.[6] Its elimination profile, pronounced binding to plasma protein and erythrocytes, and low oral bioavailability make it a suitable candidate for topical use.[6] S0597 has shown a favorable safety profile in preclinical and phase 1 clinical development (data on file, Sun Pharma Advanced Research Company). The aim of this study was to assess the clinical efficacy, safety, and tolerability of 3 twice-daily doses (100, 200, and 400 μg) of S0597 nasal spray compared with placebo in an environmental challenge chamber (ECC) in patients with seasonal AR (SAR). The ECC is an accepted model for testing anti-allergic treatment in early clinical

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Table 1
Baseline characteristics and reasons for discontinuation (safety population)

Characteristic	S0597			Placebo (n = 40)	Total (n = 159)
	200 μg/d (n = 39)	400 μg/d (n = 40)	800 μg/d (n = 40)		
Age (y), mean (SD)	39.0 (11.4)	37.2 (9.5)	37.2 (11.5)	37.9 (12.1)	37.8 (11.1)
Height (cm), mean (SD)	175.4 (7.4)	178.3 (7.8)	174.1 (9.0)	175.4 (9.7)	175.8 (8.6)
Weight (kg), mean (SD)	78.7 (18.0)	78.6 (14.3)	74.9 (13.3)	79.7 (12.1)	77.9 (14.5)
Sex, n (%)					
Men	20 (51.3)	26 (65.0)	19 (47.5)	22 (55.0)	87 (54.7)
Women	19 (48.7)	14 (35.0)	21 (52.5)	18 (45.0)	72 (45.3)
White race, n (%)	39 (100.0)	40 (100.0)	40 (100.0)	40 (100.0)	159 (100.0)
Discontinuation of study, n (%)	0 (0.0)	4 (10.0)	2 (5.0)	1 (2.5)	7 (4.4)
AE	0 (0.0)	4 (10.0)	1 (2.5)	1 (2.5)	6 (3.8)
Other	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.6)

Abbreviation: AE, adverse event.

development.[7] A particular advantage of the ECC is the ability to control environmental conditions, such as temperature, humidity, and allergen concentration. As a result, fewer participants are necessary to show significant treatment effects than would be required for a field study. Numerous clinical trials in Europe, North America, and Japan have used ECCs to test anti-allergic treatment, including INS.[8–16]

Methods

Study Design

This was a phase 2, randomized, double-blinded, placebo-controlled, single-center, 4-arm, parallel study conducted at the Fraunhofer Institute for Toxicology and Experimental Medicine (Hannover, Germany). Adults with SAR were repeatedly exposed to grass pollen (*Dactylis glomerata*; Allergon AB, Ängelholm, Sweden) in the ECC (4,000 grains/m^3). The concentration of pollen in the ECC was closely monitored and stable for the duration of the challenges.[12]

The study was performed from July to November 2012 (the first subject was enrolled on July 9, 2012 and the last subject completed the study on November 2, 2012). Therefore, the study began after the peak of the grass pollen season in Germany (which occurs in May or June). After a screening visit, including a 2-hour screening pollen challenge, the patients attended a 4-hour baseline pollen challenge on day 1, after which each patient received S0597 at a dose of 200 μg/d (100 μg twice daily), 400 μg/d (200 μg twice daily), or 800 μg/d (400 μg twice daily) or placebo as a nasal spray (morning and evening) for 15 days (days 1–15). On day 1, the patients received the morning dose after the challenge under the supervision of an investigator and took the evening dose at home as late as possible. On days 2 to 14, the patients were self-dosed twice a day, morning and evening, with approximately 12 hours between doses (patients were instructed to adhere to a 12-hour dosing cycle whenever possible). On days 15 and 16, a 4-hour pollen challenge was performed to evaluate treatment efficacy. On day 15, the patients received the morning dose 30 minutes before the challenge and took the last treatment dose at home in the evening, 12 hours before the day 16 challenge.

After each challenge, patients were provided with a terbutaline Turbohaler (Bricanyl Turbohaler, AstraZeneca, London, United Kingdom) as rescue medication. Patients were instructed to use rescue medication if there was a decrease of at least 20% in lung function.

This study was approved by the local competent authority and the ethics committee of the Hannover Medical School (Hannover, Germany). It was conducted in accordance with the Declaration of Helsinki (Somerset West Amendment, 1996) and the International Conference on Harmonisation Guidelines on Good Clinical Practice. Written informed consent was obtained from all study participants, the consent form for which had been approved by the ethics committee. The ClinicalTrials.gov identifier is NCT01614691.

Patients

Patients were 18 to 65 years old and had a history of SAR from grass pollen; a positive skin prick test reaction to *D glomerata* within 12 months before enrollment; a total nasal symptom score (TNSS) of at least 6 during a 2-hour screening challenge in the ECC; forced expiratory volume in 1 second greater than 80% predicted; and were nonsmoking for at least 12 months before enrollment, with a smoking history shorter than 10 pack-years.

The main exclusion criteria included a history or the presence of perennial AR; clinically significant nasal septum deformation or nasal polyps; respiratory tract infection within 2 weeks before the screening challenge; pulmonary disease other than mild intermittent asthma controlled by using β_2-agonists alone; history of cataract, glaucoma, or ocular hypertension; anti-allergy immunotherapy within 2 years

Table 2
Change in TNSS from baseline to day 15 and day 16 (intent-to-treat population)

	S0597			Placebo (n = 39)	*P* value
	200 μg/d (n = 39)	400 μg/d (n = 37)	800 μg/d (n = 39)		
Baseline TNSS, mean (SD)	5.8 (1.62)	6.3 (1.67)	6.1 (1.72)	5.5 (1.80)	—
Change from baseline to day 15, LSM (SE)	−2.49 (0.268)	−2.61 (0.276)	−2.75 (0.268)	−1.72 (0.270)	.0005
Change from baseline to day 16, LSM (SE)	−1.97 (0.284)	−2.03 (0.298)	−2.49 (0.288)	−0.56 (0.286)	.0005
P value for pairwise comparison[a]	.0025	.0016	<.001	—	—
Change from baseline to day 15 and day 16 (%)					
Day 15, n	39	37	39	39	—
Change from baseline (%), mean (SD)	−37.6 (34.05)	−45.1 (25.42)	−45.7 (27.93)	−25.2 (34.07)	
Day 16, n	39	36	38	39	—
Change from baseline (%), mean (SD)	−32.0 (31.23)	−35.0 (29.59)	−41.8 (29.70)	−2.9 (43.47)	

Abbreviations: LSM, least-squares mean; TNSS, total nasal symptom score.
[a]Significant paired treatment difference vs placebo (by the Student *t* test).

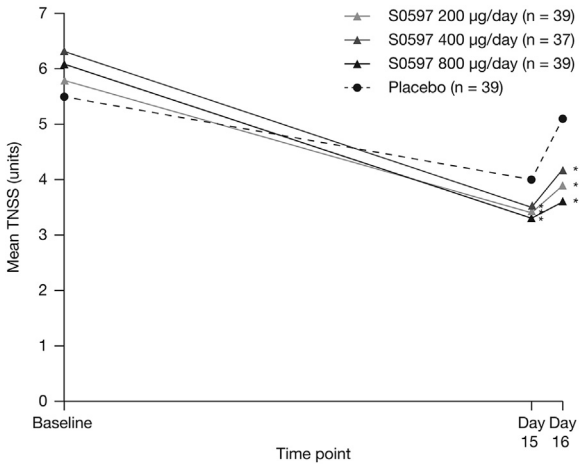

Figure 1. Total nasal symptom score (TNSS) for the intent-to treat population. *$P < .05$ vs placebo.

before screening; treatment with corticosteroids within 4 weeks before screening; treatment with oral H_1 antihistamines, cromoglycates, leukotriene modifiers, or topical decongestants within 72 hours before screening; treatment with a β-blocker or other medication that might interfere with rescue medication for allergic shock within 1 week before screening; and participation in another clinical trial within 30 days before screening.

Before screening, there was a 4-week washout period for systemic, topical, nasal, and inhaled corticosteroids, with a 72-hour washout for H_1 antihistamines, cromoglycates, leukotriene modifiers, and topical decongestants.

Assessments

Nasal symptoms

The primary efficacy end point was change in TNSS from baseline to days 15 and 16. Nasal symptoms (congestion, rhinorrhea, sneezing, itching) were self-assessed before and every 20 minutes throughout the allergen challenge in the ECC. For each symptom, patients recorded scores according to the following 4-point severity scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The TNSS was calculated by adding the scores of the 4 individual nasal subscales.

Change in TNSS subscales from baseline to days 15 and 16 comprised the secondary efficacy end point.

Nasal secretion

Change in nasal secretion from baseline to days 15 and 16 was an additional secondary end point and determined using pre-weighed paper tissues. Used and unused tissues were saved in a plastic bag by each patient and collected every 60 minutes. The amount of nasal secretion was determined by weighing the paper tissues.

Safety

Safety was assessed as the incidence and intensity of adverse events (AEs), vital signs (pulse rate and blood pressure), lung function (forced expiratory volume in 1 second), and physical examination.

Statistical Analyses

Approximately 320 patients were planned to be screened to randomize 160 patients to the study. The following populations were analyzed.

Safety population—all randomized patients receiving at least 1 dose of the study treatment or placebo.

Intent-to-treat population—all patients who were randomized and received at least 1 dose of the study treatment and had baseline and at least 1 post-baseline efficacy assessments.

Per-protocol (PP) population—all patients who completed the study without any major protocol deviations.

The primary and secondary efficacy analyses were conducted for the intent-to-treat population using the last observation carried forward method. Least-squares mean changes in TNSS, TNSS subscales, and nasal secretion from baseline to days 15 and 16 were compared among groups using repeated-measures analysis of covariance, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline value as the covariate (treatment comparison at the 2-sided .05 significance level). Pairwise treatment comparisons of each dose of S0597 vs placebo also were conducted using the Student t test. All statistical analysis was performed using SAS 9.2 or subsequent versions (SAS Institute, Cary, North Carolina).

A supportive analysis for the primary and secondary end points was performed for the PP population.

Results

Study Population

A total of 159 patients (mean age 37.8 years; 54.7% men; 99.4% white) were randomized to receive study medication. All patients had a positive skin prick test reaction to *D glomerata*. Baseline characteristics are listed in Table 1.

Altogether, 152 patients (95.6%) completed the study. Seven patients discontinued the study (6 [3.8%] owing to AEs; 1 [0.6%] withdrew voluntarily). In total, 154 patients were included in the intent-to-treat population.

Nasal Symptoms

Mean TNSS scores at baseline were 5.8 in the S0597 200-µg/d group, 6.3 in the 400-µg/d group, 6.1 in the 800-µg/d group, and 5.5 in the placebo group (Table 2). For the primary efficacy end point, there was a statistically significant improvement in TNSS in all active treatment groups vs placebo from baseline to days 15 and 16 ($P = .0005$ overall; Table 2, Fig 1). Mean percentage decreases in TNSS from baseline to day 15 were in the range of 38% to 46% in the active treatment groups compared with

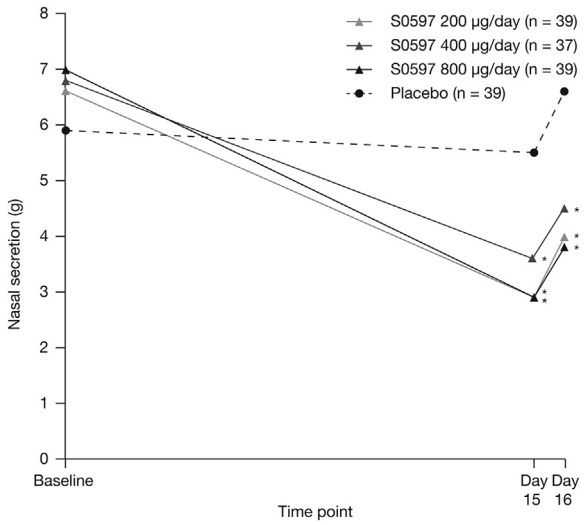

Figure 2. Effect of treatment on nasal secretion in the intent-to treat population. *$P < .0001$ vs placebo.

Table 3
Summary of AEs (safety population)

	S0597			Placebo (n = 40)
	200 μg/d (n = 39)	400 μg/d (n = 40)	800 μg/d (n = 40)	
AEs, n (%)	32 (23.1)	28 (19.3)	46 (31.7)	39 (26.9)
Serious AEs, n (%)	0	1 (0.7)	0	0
AEs leading to death, n (%)	0	0	0	0
AEs leading to permanent discontinuation of study drug, n (%)	0	3 (2.1)	1 (0.7)	1 (0.7)
AEs leading to withdrawal of patient, n (%)	0	4 (2.8)	1 (0.7)	1 (0.7)
AEs related to study drug, n (%)	16 (11.1)	8 (5.5)	19 (13.1)	16 (11.0)
Severity of study drug-related AEs, n (%)				
Mild	15 (10.3)	8 (5.5)	15 (10.3)	15 (10.3)
Moderate	1 (0.7)	0	4 (2.8)	1 (0.7)
Severe	0	0	0	0
Treatment-emergency AEs (≥2 by preferred term), n (%)				
Headache	10 (7.8)	7 (5.4)	16 (12.4)	13 (10.1)
Paresthesia	0	0	2 (1.6)	2 (1.6)
Oropharyngeal pain	1 (0.8)	2 (1.6)	1 (0.8)	1 (0.8)
Epistaxis	2 (1.6)	1 (0.8)	0	0
Nasal mucosal disorder	2 (1.6)	0	0	0
Nasopharyngitis	2 (1.6)	2 (1.6)	0	0
Upper respiratory tract infection	0	2 (1.6)	0	1 (0.8)
Herpes simplex	0	0	0	2 (1.6)
Nausea	0	0	2 (1.6)	2 (1.6)
Back pain	0	2 (1.6)	0	0
Conjunctivitis allergic	0	0	1 (0.8)	2 (1.6)
Dysmenorrhea	2 (1.6)	0	0	0

Abbreviation: AEs, adverse events.

25% in the placebo group; on day 16, these percentage decreases in TNSS ranged from 32% to 42% in the 3 S0597 groups vs just 3% in the placebo group (Table 2). Improvements in TNSS were related to dose, with greater decreases in TNSS observed in the highest-dose (800-μg/d) group ($P < .0001$ vs placebo). The primary end point findings were confirmed in the PP population.

For the secondary efficacy end point of TNSS subscales, statistically significantly greater decreases (improvements) from baseline to days 15 and 16 in nasal congestion ($P = .0012$ overall), rhinorrhea ($P = .0011$ overall), nasal itching ($P = .0201$ overall), and sneezing scores ($P = .0023$ overall) were observed vs placebo in each of the active treatment groups (eTable 1). These findings also were observed in the PP population.

Nasal Secretion

The overall mean (SD) values for nasal secretion at baseline were 6.65 g (4.14) in the S0597 200-μg/d group, 6.76 g (4.71) in the 400-μg/d group, 6.98 g (3.89) in the 800-μg/d group, and 5.89 g (4.69) in the placebo group.

There was a statistically significant decrease in nasal secretion from baseline to days 15 and 16 in each of the active treatment groups compared with placebo ($P < .0001$ for all comparisons; Fig 2). Decreases in nasal secretion from baseline to days 15 and 16 were related to dose, with the highest-dosage group (800 μg/d) achieving the greatest decreases compared with placebo (day 15, −3.83 g change from baseline vs −0.77 g, respectively, $P < .0001$; day 16, −3.06 g change from baseline vs 0.39 g, respectively, $P < .0001$, least-squares mean values).

Safety

S0597 was well tolerated at all doses studied. A total of 145 AEs were reported during the study (Table 3), most of which were mild (68.3%) or moderate (27.6%) in intensity. One serious AE of cartilage injury (non-nasal) occurred in a patient randomized to the S0597 400-μg/d group. This was not considered related to the study medication.

Of the 59 AEs that were considered to be related to the drug, 19 events (32.2%) occurred in the S0597 800-μg/d group, 16 events (27.1%) occurred each in the S0597 200-μg/d and placebo groups, and 8 events (13.6%) events occurred in the S0597 400-μg/d group. The most commonly reported study drug-related AE was headache (10 events in the 200-μg/d group [7.8%], 7 in the 400-μg/d group [5.4%], 16 in the 800-μg/d group [12.4%], and 13 in the placebo group [10.1%]).

One patient in the S0597 800-μg/d group was administered rescue medication for mild bronchoconstriction. This was successfully treated with a β_2-agonist and the patient recovered completely on the same day. No study-related AEs were serious or led to death, permanent discontinuation of the study drug, or withdrawal of the patient from the study.

No treatment-related findings were observed for vital signs, lung function, or physical examination.

Discussion

In this 15-day, randomized, placebo-controlled, double-blinded, parallel group, single-center study, the dose-related efficacy and safety of S0597, a novel INS, were assessed in patients with SAR using repeated grass pollen challenges in an ECC. Participants were repeatedly exposed to grass pollen (*D glomerata*) in the ECC at a concentration of 4,000 grains/m^3. In a validation study using the ECC, a dose-dependent induction of allergic symptoms was observed when participants were exposed to pollen concentrations of 1,000 to 8,000 grains/m^3, which were noted to be within or above the upper range of naturally occurring grass pollen in Europe.[12] Based on the results of the validation study, a concentration of 4,000 grains/m^3 was chosen for use in all subsequent studies because, with this concentration, most subjects showed at least moderate symptoms (ie, a TNNS of 6 of 12). In the area around the Fraunhofer Institute, pollen concentrations of 2,100 grains/m^3 have been measured in season.[12] Although the concentration of 4,000 grains/m^3 used in the present study was higher than the natural exposure, patients developed moderate symptoms.

All 3 doses of S0597 (200, 400, and 800 μg/d) showed a significant decrease in nasal symptoms (TNSS) compared with placebo on days 15 and 16. This also was true for the assessment of nasal secretion, which decreased significantly with all 3 doses of S0597

compared with placebo on days 15 and 16, with the greatest decrease observed in the highest-dose group.

A large placebo effect in TNSS was observed on day 15, with a change from baseline of −25.2%. However, on day 16, the change from baseline in the placebo group was only −2.9%. This placebo effect could not be observed in the objective measurement of nasal secretion. The amount of nasal secretion was +15.8% on day 15 and +58.0% on day 16 compared with baseline. The increase in nasal secretion and decreased placebo effect on day 16 compared with day 15 is likely due to a priming effect, which also has been observed in other studies of repeated allergen challenges.[8,9,11–13,17] In the present study, the priming effect was efficiently prevented by S0597.

Interestingly, and in contrast to the objective measurement of nasal secretion, patients in the placebo group reported a decrease in the subjective symptom of rhinorrhea. The scores (mean ± SD) for rhinorrhea in the placebo group were 1.7 ± 0.5 at baseline, 1.2 ± 0.5 on day 15, and 1.4 ± 0.6 on day 16. This demonstrates the importance of an objective measurement such as nasal secretion, which can be used to support subjective results or to put them into perspective. An additional objective measurement often used in ECC studies is rhinomanometry, which is used to assess nasal flow and degree of nasal obstruction.[18–20]

Similar to other new INS therapies, S0597 was well tolerated and demonstrated a good safety profile. The most common AE of headache did not show a relation to dose and was more frequent in the placebo group than in the S0597 200- and 400-μg/d groups. The high frequency of this AE probably was caused by the allergen challenge.

Unlike some other corticosteroids, which generally act non-selectively, S0597 has shown potent glucocorticoid receptor binding and low binding affinity to other sex steroid receptors and aldosterone.[6] Furthermore, in preclinical models, S0597 has shown local anti-inflammatory activity, low oral bioavailability, and low potential for systemic adverse effects, leading to a high therapeutic index.[6] These findings together with the present results suggest that S0597 compares favorably with existing INS therapies in efficacy and side effects. However, further studies are needed to make head-to-head comparisons.

In conclusion, this study demonstrated that all 3 tested doses of S0597 were safe, well tolerated, and showed a significant treatment benefit compared with placebo in decreasing the symptoms of SAR in adult patients. Additional clinical trials are needed to assess whether S0597 also is suitable as a once-daily treatment.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2015.07.016.

References

[1] Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24:758–764.
[2] Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160.
[3] Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466–476.
[4] Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. *J Allergy Clin Immunol*. 1999;104:S150–S158.
[5] Blaiss MS. Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc*. 2011;32:413–418.
[6] Thennati R, Khanna A, Khanna M, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of compound SFDAC by intranasal administration of multiple escalating dose in healthy male subjects. *Clin Pharmacol Drug Dev*. 2014;3:428–438.
[7] Krug N, Badorrek P, Hohlfeld JM. Experience with an allergen challenge chamber for clinical trials in allergic rhinitis. *Clin Exp Allergy Rev*. 2012;12:14–19.
[8] Bernstein JA, Salapatek AM, Lee JS, et al. Provocation of nonallergic rhinitis subjects in response to simulated weather conditions using an environmental exposure chamber model. *Allergy Asthma Proc*. 2012;33:333–340.
[9] Day JH, Briscoe MP, Rafeiro E, et al. Onset of action of intranasal budesonide (Rhinocort aqua) in seasonal allergic rhinitis studied in a controlled exposure model. *J Allergy Clin Immunol*. 2000;105:489–494.
[10] Hashiguchi K, Tang H, Fujita T, et al. Bepotastine besylate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO Chamber). *Expert Opin Pharmacother*. 2009;10:523–529.
[11] Jacobs RL, Harper N, He W, et al. Effect of confounding cofactors on responses to pollens during natural season versus pollen challenge chamber exposure. *J Allergy Clin Immunol*. 2014;133:1340–1346.
[12] Krug N, Hohlfeld JM, Larbig M, et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy*. 2003;33:1667–1674.
[13] Krug N, Hohlfeld JM, Geldmacher H, et al. Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. *Allergy*. 2005;60:354–359.
[14] Krug N, Gupta A, Badorrek P, et al. Efficacy of the oral chemoattractant receptor homologous molecule on TH2 cells antagonist BI 671800 in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2014;133:414–419.
[15] Patel D, Garadi R, Brubaker M, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients: olopatadine hydrochloride versus mometasone furoate monohydrate. *Allergy Asthma Proc*. 2007;28:592–599.
[16] Zieglmayer P, Zieglmayer R, Bareille P, et al. Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber. *Curr Med Res Opin*. 2008;24:1833–1840.
[17] Connell JT. Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. *J Allergy*. 1969;43:33–44.
[18] Badorrek P, Dick M, Hecker H, et al. Anti-allergic drug testing in an environmental challenge chamber is suitable both in and out of the relevant pollen season. *Ann Allergy Asthma Immunol*. 2011;106:336–341.
[19] Badorrek P, Dick M, Emmert L, et al. Pollen starch granules in bronchial inflammation. *Ann Allergy Asthma Immunol*. 2012;109:208–214.
[20] Hohlfeld JM, Holland-Letz T, Larbig M, et al. Diagnostic value of outcome measures following allergen exposure in an environmental challenge chamber compared with natural conditions. *Clin Exp Allergy*. 2010;40:998–1006.

eTable 1
Change in total nasal symptom score subscales from baseline to day 15 and day 16 (intent-to-treat population)

	S0597			Placebo (n = 39)	*P* value
	200 μg/d (n = 39)	400 μg/d (n = 37)	800 μg/d (n = 39)		
Nasal congestion					.0012
Change from baseline to day 15, LSM (SE)	−0.84 (0.084)	−0.79 (0.087)	−0.85 (0.084)	−0.52 (0.085)	
Change from baseline to day 16, LSM (SE)	−0.71 (0.089)	−0.66 (0.094)	−0.81 (0.090)	−0.30 (0.090)	
P value for pairwise comparison[a]	.0012	.0078	.0003	—	—
Rhinorrhea					.0011
Change from baseline to day 15, LSM (SE)	−0.61 (0.074)	−0.63 (0.076)	−0.68 (0.074)	−0.38 (0.075)	
Change from baseline to day 16, LSM (SE)	−0.47 (0.077)	−0.38 (0.080)	−0.56 (0.078)	−0.10 (0.077)	
P value for pairwise comparison[a]	.0022	.0083	.0002	—	—
Nasal itching					.0201
Change from baseline to day 15, LSM (SE)	−0.61 (0.079)	−0.63 (0.082)	−0.69 (0.079)	−0.48 (0.079)	
Change from baseline to day 16, LSM (SE)	−0.48 (0.086)	−0.54 (0.090)	−0.62 (0.087)	−0.16 (0.087)	
P value for pairwise comparison[a]	.0356	.0204	.0032	—	—
Sneezing					.0023
Change from baseline to day 15, LSM (SE)	−0.43 (0.068)	−0.57 (0.070)	−0.53 (0.068)	−0.34 (0.068)	
Change from baseline to day 16, LSM (SE)	−0.33 (0.080)	−0.44 (0.083)	−0.49 (0.081)	−0.01 (0.080)	
P value for pairwise comparison[a]	.0356	.0008	.0011	—	—

Abbreviation: LSM, least-squares mean.
[a]Significant paired treatment difference vs placebo (by the Student *t* test).